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Autonomic Nervous System Activity and the Spontaneous Initiation of Ventricular Tachycardia

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Objectives. **We hypothesized that neurohormonal activity contributes to the initiation of sustained ventricular tachycardia (VT) as reflected in indices of heart rate variability (HRV).**

Background. **Autonomic nervous system activity participates in experimental arrhythmias but clinical studies have been inconsistent.**

Methods. **Holter electrocardiograms from 53 patients with VT were analyzed. Heart rate variability indices were determined over 5 and 15 min and 24 h and examined for changes before the onset of VT. Heart rate variability indices in the frequency domain included ultra low frequency power (FP) (ULFP): 0–0.0033 Hz; very low FP (VLFP): 0.0033–0.04 Hz; low FP (LFP): 0.04–0.15 Hz; high FP (HFP): 0.15–0.4 Hz; total power (TP); normalized LFP (LFP_n); normalized HFP (HFP_n), and the ratio: LFP/HFP.**

Results. **Heart rate variability indices were severely diminished: TP: 12,009 ± 11,076 ms^2; ULFP: 10,087 ± 9,565 ms^2; VLFP: 1,416 ± 1,571 ms^2; LFP: 544 ± 620 ms^2; HFP: 161 ± 176 ms^2, and LFP/HFP: 3.68 ± 2.83. Heart rate increased before VT (80.4 ± 17.3 to 85.3 ± 17.4 bpm, $p < 0.001$). Several HRV variables declined 30 min before VT compared to 24-h values (VLFP: −5.89 ± 17.81%, $p = 0.031$; LFP: −5.23 ± 14.3%, $p = 0.003$; HFP: −4.35 ± 13.7%, $p = 0.04$). LFP_n and the LFP/HFP ratio decreased significantly before the onset of VT (−17.7 ± 46.9%, $p = 0.035$ and −8.24 ± 38.8%, $p = 0.037$, respectively), whereas HFP_n increased slightly (4.29 ± 29.9%, $p = 0.097$).**

Conclusions. **Heart rate rose, whereas LFP, LFP_n and LFP/HFP fell before the onset of VT. This pattern of changes could be explained by a rise in sympathetic activity and saturation of the HRV signal resulting in dissociation of the average and rhythmical effects of sympathetic activity. These findings suggest that alterations in autonomic activity contributed to arrhythmogenesis in this group of patients.**

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Participation of the autonomic nervous system in the genesis of ventricular tachyarrhythmias and sudden cardiac death is well documented (1). In animal models increased sympathetic activity reduces the ventricular fibrillation threshold (2) and provokes ventricular arrhythmias (3,4), particularly in the presence of myocardial ischemia (5,6). A protective effect is exerted by increased vagal activity (7,8), and is most pronounced in the presence of elevated sympathetic tone (9). There is also convincing evidence for a relation between autonomic nervous system function and clinical events; elevated norepinephrine levels (10) and increased sympathetic nerve activity (11) are associated with a poor prognosis, whereas treatment with beta-adrenergic receptor blockers reduces mortality after myocardial infarction (12).

Despite progress, however, major gaps in our understanding of the effects of neurohormonal activity on the generation of clinical ventricular arrhythmias persist. Several temporal modes of influence can be proposed, each with distinct clinical implications. One possibility is that short-term changes, for example, a rise in sympathetic activity or a decline in parasympathetic tone, trigger ventricular tachyarrhythmias in the setting of the appropriate anatomic or functional alterations in the myocardium. Another possibility is that short-term changes have no effect, but chronic alterations cause remodeling, that is, slowly progressive proarrhythmic alterations in myocyte structure and function (13,14). Still another possibility is that elevated sympathetic activity and reduced vagal tone create the necessary conditioning effects on myocardium for arrhythmias to occur independent of long- or short-term effects (15).

Analysis of spontaneous ventricular arrhythmias could pro-

*Electrophysiologic Study Versus Electrocardiographic Monitoring Trial. The list of investigators appears in reference number 35.

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Abbreviations and Acronyms

ANOVA	=	analysis of variance
ESVEM	=	Electrophysiologic Study Versus Electrocardiographic Monitoring
HFP	=	high frequency power
HFP_n	=	normalized high frequency power
HR	=	heart rate
HRV	=	heart rate variability
LFP	=	low frequency power
LFP_n	=	normalized low frequency power
pNN50	=	percentage of differences between adjacent normal RR intervals that are >50 ms
r-MSSD	=	square root of the mean of the squared differences between adjacent normal RR intervals
SDANN	=	standard deviation index of the average normal RR-intervals for all 5-minute segments
SDANN index	=	SD of the average normal RR intervals for all 5 minute segments
SDNN	=	standard deviation (SD) of normal RR-intervals in the entire 24-hour ECG recording
SDNN index	=	mean of the SDs of normal RR-intervals for all 5-minute segments
TP	=	total power
ULFP	=	ultra low frequency power
VLFP	=	very low frequency power
VT	=	Sustained monomorphic ventricular tachycardia

vide information about triggers of arrhythmias unobtainable from experimental models or electrical induction of arrhythmias. We (16,17) and others (18–23) have reported that isolated and repetitive ventricular ectopic beats rarely resemble sustained ventricular tachycardia induced by programmed electrical stimulation, and that many episodes of spontaneous sustained ventricular tachycardia (VT) appear to arise de novo late in the cardiac cycle in the absence of an identifiable trigger. Although a number of mechanisms including concealed extrasystoles, sinus beat reentry or occult ischemia could explain these findings, it is also possible that neurohormonal activity is partly responsible for precipitating VT in the absence of overt electrocardiographic changes. It should be stressed that the electrocardiographic records of such events rarely demonstrate ST segment shifts or T-wave changes that might indicate myocardial ischemia (17–23).

Advances in heart rate variability (HRV) analysis have provided powerful methods for assessing autonomic nervous system activity in a wide variety of clinical settings (24–26), although the interpretation of specific indices remains controversial (27). Studies in experimental animals have demonstrated a short-term relation between autonomic nervous system activity and arrhythmogenesis using HRV analysis (28). Studies of patients after myocardial infarction have validated the use of indices of HRV for predicting long-term outcome (29–31). However, studies of short-term (hours to minutes) changes in HRV indices of autonomic activity before the onset of spontaneous VT in small groups of patients have been inconsistent (32–34).

The purpose of this study was to examine the influence of autonomic nervous system activity on the initiation of sustained ventricular tachyarrhythmias by examining the heart rate and heart rate variability preceding VT. Several previous studies were based on recordings collected during the course of routine clinical practice. In contrast, our study included a relatively large number of patients whose data were collected in a uniform, prospective manner during the course of a clinical trial conducted at 14 clinical centers (35–37). This could lessen the chance that the circumstances of the recordings or types of patients included are biased by local practice patterns, and it could enhance the homogeneity and reliability of the findings.

Methods

Patients. Patients for this study were identified by the presence of spontaneous, sustained (≥30 s, rate >100 bpm) VT on a 24-h Holter recording. The Holter tapes were obtained from the ESVEM trial, which has been described in detail (35–37). Patients considered for this trial had a history of cardiac arrest, documented ventricular fibrillation, sustained ventricular tachycardia, or syncope. Patients with recent myocardial infarction, the long QT syndrome, hypertrophic cardiomyopathy or arrhythmias due to transient or reversible disorders were excluded. Enrolled patients had at least 10 premature ventricular complexes per hour and inducible sustained ventricular tachyarrhythmias (35).

Analysis of recordings. The Holter recordings were obtained at least five half-lives after the discontinuation of antiarrhythmic drugs. Baseline Holter monitor recordings (1,646 tapes) were obtained in 868 of the 2,103 patients screened for the trial (36). The tapes were analyzed and verified as described previously (35). Tapes from 59 patients demonstrated VT; six with atrial fibrillation were excluded. Episodes of VT from a single patient may have common features, and patients with multiple episodes of VT could differ from patients with a single episode of VT. Therefore, inclusion of multiple episodes of VT from individual patients would favor characteristics of patients with more episodes. To avoid this potential bias, the analysis was restricted to one VT episode (the longest) per patient.

Electrocardiographic data were digitized at 400 Hz. QRS complexes were detected and classified on a commercial system (Burdick, Inc., Milton, WI) using custom software and verified by a cardiologist. Intervals between normal QRS complexes were extracted, and a regularly spaced time series was sampled at a frequency of 2 Hz using a "boxcar" low-pass filter (38). Gaps in the time series resulting from noise or ectopic beats were filled in with linear splines, which can cause a small reduction in high frequency power but do not affect other components of the power spectrum (39). In some previous studies, tapes with frequent ectopy were excluded. However, this could result in a selection bias or loss of important data. For instance, restriction of data sets to >85% normal beats would have excluded 40% of the data files. To assess the impact of including segments with ectopic activity,

Table 1. Clinical Characteristics of Patients With and Without Recorded Spontaneous Ventricular Tachycardia

	Study	All SpVT	No SpVT	p*	p†
Number in each group‡	n = 53	n = 59	n = 440		
Age (years)	64.1 ± 10.3	64.5 ± 10.3	64.5 ± 9.7	0.61	0.99
Female	7 (13)	9 (15)	55 (13)	0.42	0.56
Presenting event					
VF or sudden death	6 (11)	7 (11)	98 (22)	0.14	0.051
VT or syncope	47 (89)	52 (88)	342 (78)		
Ischemic heart disease	44 (83)	47 (80)	373 (85)	0.14	0.37
Years since last MI mean	5.7 ± 6.7	5.9 ± 6.8	8.3 ± 8.3	0.13	0.049
(median)	(2.5)	(2.5)	(6.4)		
SAS class 3 or 4	14 (26)	16 (27)	134 (30)	0.82	0.59
Ejection fraction (%)	36 ± 15	35 ± 2	32 ± 12	0.10	0.11
PVC/h on Holter	419 ± 541	371 ± 505	304 ± 385	0.12	0.2
(median)	(179)	(151)	(170)		
Digitalis	10 (25)	14 (30)	165 (38)	0.09	0.34
Verapamil or diltiazem	6 (15)	6 (13)	63 (14)	0.39	0.81
Beta-blocker	4 (10)	5 (11)	59 (13)	0.79	0.62

*This group versus patients without spontaneous VT. †Patients with spontaneous VT versus patients without spontaneous VT. ‡Percentages are in parentheses except where indicated, and reflect missing data for some variables. Beta-blocker = beta-adrenergic receptor blocking drug; MI = myocardial infarction; PVC = premature ventricular complexes; SAS = Symptomatic Activity Scale; SpVT = spontaneous sustained monomorphic VT; VF = ventricular fibrillation; VT = ventricular tachycardia.

we repeated the analyses using intervals with >50%, >75% or >85% of normal beats.

RR intervals were analyzed in time and frequency domains over 5- and 15-min intervals and over the entire 24-h period.

Time domain analysis. Mean and standard deviation of normal RR intervals, the square root of the mean of the squared differences between adjacent normal RR intervals and percentage of differences between adjacent normal RR intervals >50 ms were estimated in each 5- and 15-min interval (40).

Frequency domain analysis. After subtracting the mean from the time series, power spectral analysis of HRV was performed using fast Fourier transform and a Hanning window. Zero padding was applied to increase the outcome frequency resolution, and the resulting power spectrum was corrected for the filtering and windowing (38,40). Power was integrated over each frequency range: high (HFP), 0.15–0.4 Hz; low (LFP), 0.04–0.15 Hz; total (TP), 0.01–0.4 Hz, and 0.0033–0.4 Hz for 5- and 15-min intervals, respectively; very low (VLFP), 0.0033–0.04 Hz in 15-min intervals. The ultra low frequency component (ULFP), 0–0.0033 Hz, was determined over 24 h. The ratio of low and high frequency power was calculated. Normalized values were obtained by calculating the fraction of LFP and HFP variability with respect to the sum of LFP + HFP.

Statistical analysis. Shapiro–Wilks' *W* test of normality was used to assess distribution of the data. Because of substantial deviation from normal distribution, nonparametric Friedman analysis of variance (ANOVA) was applied to test the significance of changes in each variable over time. The significance of differences between 24-h averaged measures and intervals prior to VT was assessed with the Wilcoxon matched pairs test. Different groups of patients were compared using Kruskal–Wallis ANOVA. Statistical significance did not change when skewed variables were reanalyzed using logarithmically transformed data to normalize the distribution. ANOVA for repeated measurements was applied to test the significance of temporal changes in the transformed variables preceding VT. To compare the logarithmically transformed variables, *t* tests, for dependent samples were used. Results are expressed as mean ± standard deviation (SD) of the logarithmically transformed data unless otherwise indicated. Differences at $p < 0.05$ were considered significant.

Results

Clinical characteristics. The mean age of the 53 patients in this study was 63.9 ± 10.3 years, and 13% were women. The etiology of heart disease was ischemic in 83% of the patients, and the mean ejection fraction was 33.6 ± 16.8% (Table 1). The mean (±SD) duration of the index arrhythmia was 13.4 ± 24.5 min (median was 2.77 min, range 30 s to 117 min), and mean cycle length was 369 ± 83 ms (median 352 ms, range 206 to 569 ms). The frequency of VT was higher during day than during night, peaking in the morning and late afternoon (Fig. 1).

Twenty-four hour heart rate variability indices. Time domain indices of HRV were severely reduced: SDNN: 83.3 ± 40.2 ms (ln: 4.31 ± 0.49); SDANN index: 73.4 ± 36.9 ms (ln: 4.18 ± 0.50); SDNN index: 34.3 ± 19.4 ms (ln: 3.36 ± 0.62); r-MSSD: 24.4 ± 15.1 ms (ln: 3.04 ± 0.56), pNN50: 4.48 ± 5.09% (ln: 0.97 ± 1.05) (28). Frequency domain variables were similarly depressed (40): TP: 12,209 ± 11,076 ms^2 (ln: 8.88 ± 1.22); ULFP: 10,087 ± 9,565 ms^2 (ln: 8.66 ± 1.25); VLFP:

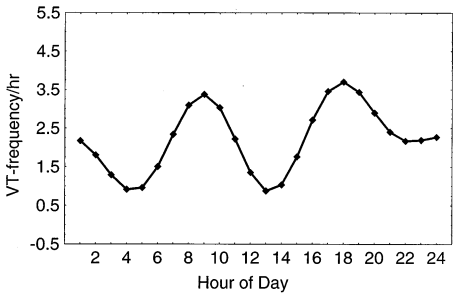


Figure 1. Circadian distribution of ventricular tachyarrhythmias (VT) in the studied group.

1,416 ± 1,571 ms^2 (ln: 6.48 ± 1.52); LFP: 544 ± 620 ms^2 (ln: 5.41 ± 1.55); HFP: 161 ± 176 ms^2 (ln: 4.49 ± 1.22), and LFP/HFP: 3.68 ± 2.83 (ln: 0.99 ± 0.96).

Heart rate before ventricular tachycardia. Heart rate was significantly higher 30 min before the onset of arrhythmia (85.3 ± 17.4 bpm) compared to 2 h before VT (80.4 ± 17.3 bpm, $p < 0.001$) or compared to the 24-h mean (80.8 ± 19.1 bpm, $p < 0.001$) (Fig. 2).

Heart rate variability before ventricular tachycardia. Time domain indices of HRV (standard deviation, r-MSSD and pNN50) did not change significantly prior to the onset of VT either by comparison of the mean 24-h value to the 30- and 60-min period before VT, or by comparison of the 30- and 60-min periods between 4 and 1 h before VT.

Frequency domain measures were lower in the 30-min period immediately preceding VT (ln TP = 6.85 ± 1.38, ln VLFP = 6.22 ± 1.82, ln LFP = 5.17 ± 1.47, ln HFP = 4.41 ± 1.15, LFP/HFP = 3.30 ± 2.42) compared to the 24-h average values (ln TP = 7.05 ± 1.10, $p = 0.061$; ln VLFP = 6.53 ± 1.32, $p = 0.031$; ln LFP = 5.47 ± 1.37, $p = 0.003$; ln HFP = 4.57 ± 0.97, $p = 0.043$; LFP/HFP = 3.85 ± 3.08, $p = 0.042$). The most prominent drop was in the LFP (Fig. 3c). Normalized LFP (LFP_n) was also lower at 30 min before VT (ln: −0.52 ± 0.55) compared to the 24-h value (ln: −0.46 ± 0.49, $p = 0.037$). Normalized HFP (HFP_n) was slightly increased at 30 min before VT (ln: −1.25 ± 0.61) compared to the 24-hour average (−1.32 ± 0.59, $p = 0.097$). The patterns of change in frequency domain variables were assessed by analysis of variance from 2 h to 30 min before onset of VT. Low frequency power and HFP declined significantly during this period ($p = 0.024$, $p = 0.022$, respectively). A marginally significant ($p = 0.098$) decline of the ratio LFP/HFP occurred, indicating that the decrease of LFP was larger than the fall in HFP.

The relationships between the changes in heart rate (HR) and the ratio LFP/HFP varied within as well as among individual patients. In Figure 4 the two variables increased concordantly several hours before VT, but 1 h before VT the changes were discordant, that is, HR increased, whereas LFP/HFP declined.

Effects of ectopic beat frequency. To assess the influence of ectopic activity on the spectral power of HRV we compared the results of analyses that included intervals with >50%, >75% or >85% of normal beats (Fig. 5). Although the absolute values of VLFP, LFP, HFP, TP and LFP/HFP, and the number of time intervals that were acceptable for analysis decreased as the threshold increased from 50% to 85%, the changes in all the spectral characteristics were similar. Thus, changing the threshold for ectopic beat frequency data segment selection did not alter the finding of significant reduction in VLFP, LFP and LFP/HFP preceding VT, and the lack of significant change in HFP variability.

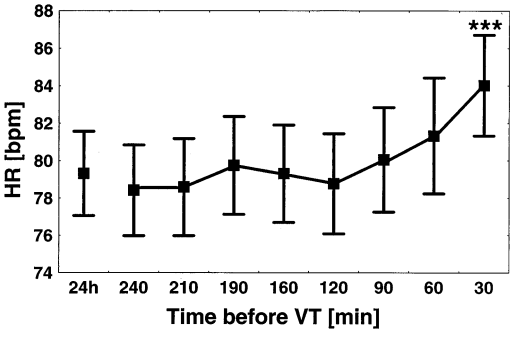
Relationship between HRV indices and clinical characteristics of patients. Mean HR over 24 h was higher in women than in men (84.8 ± 12.9 vs. 74.6 ± 14.2, $p = 0.05$). Among all the HRV indices, a correlation with borderline statistical significance with ejection fraction (33 ± 17%) was found only for the low frequency power ($r = 0.40$, $p = 0.07$). There were no other significant associations between HRV indices and age, gender, ejection fraction or the number of ectopic beats.

Discussion

Main results. The patients included in this investigation were referred for evaluation and management of known or suspected sustained ventricular tachyarrhythmias. We analyzed all Holter tapes acquired for the baseline evaluation of the ESVEM trial, and included all patients in sinus rhythm with a recorded episode of VT. The patients in this study had significant structural heart disease due, in most cases, to previous myocardial infarction. The patients in this study were not found to differ from the other patients enrolled in the ESVEM trial with respect to numerous prospectively collected clinical variables (17,37). The most important finding was evidence of significant changes in autonomic activity preceding the onset of VT.

Previous studies. Controversy exists regarding heart rate increases and the implications for changes in autonomic activity before the onset of spontaneous ventricular tachyarrhythmias. Increases in heart rate preceding the onset of sustained ventricular tachyarrhythmias have been observed in a number of studies (19,33,41–43), but not in others (21,44,45). Leclercq and colleagues noted that heart rate declined before the onset

Figure 2. Heart rate (HR). Mean of 24-h and 30-min averages before the onset of ventricular tachycardia (VT). ***The differences are significant at $p < 0.001$ compared to the 24-h average.



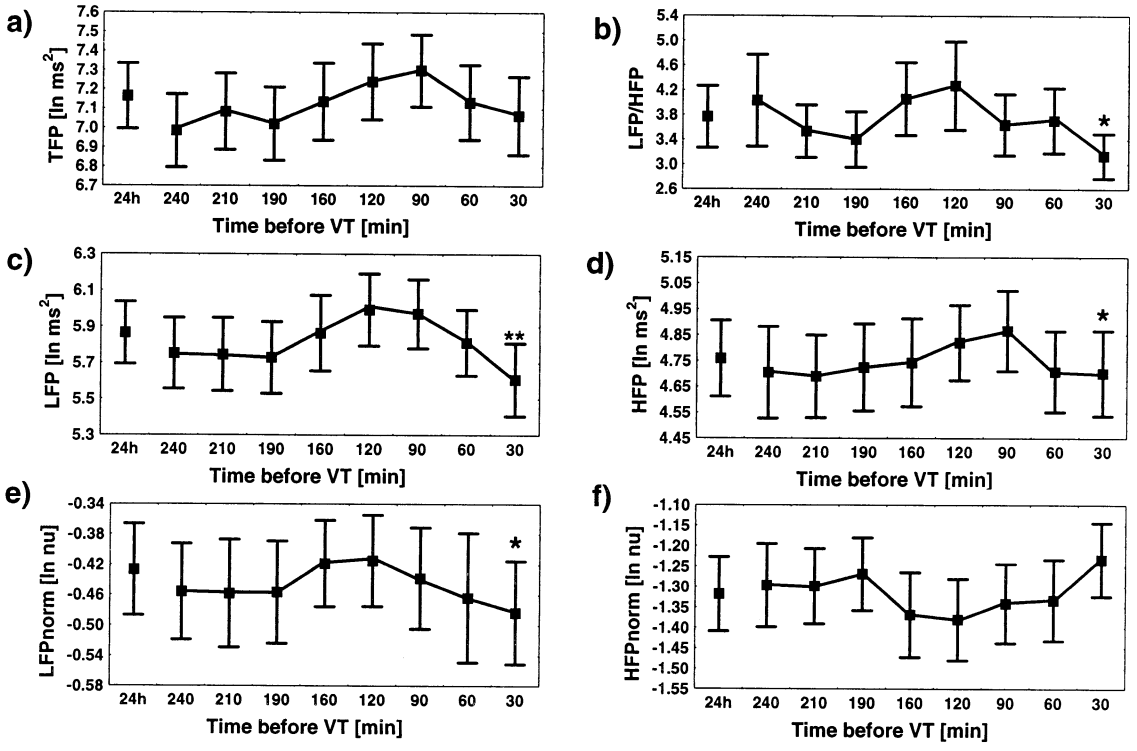


Figure 3. Frequency components of the heart rate variability signal, 24-h average and at 30-min intervals before the onset of sustained ventricular tachycardia. (**a**) Total power (TFP). (**b**) Ratio of low to high frequency power (LFP/HFP). (**c**) Low frequency power. (**d**) High frequency power. (**e**) Normalized low frequency power. (**f**) Normalized high frequency power. *$p < 0.05$ for comparison 30-min versus 24-h average. **$p < 0.01$ compared to the 24-h average. nu = normalized units. Significance of changes during 2-h period before ventricular tachycardia was assessed by analysis of variance and is discussed in the text.

of ventricular fibrillation that was initiated by drug-induced torsade de pointes ventricular tachycardia. However, they found that heart rate increased before other types of onset of ventricular fibrillation, and they attributed this effect to a rise in sympathetic activity (19). The magnitude of the rise they observed (83 to 92 bpm) was very similar to the change in heart rate found in the present investigation. This not only supports the consistency of our findings, but suggests that our observations may apply to other forms of ventricular tachyarrhythmias.

Although heart rate increases before ventricular tachyarrhythmias have been interpreted by several investigators as indicating an increase in sympathetic tone (19,34,41,43), heart rate is a relatively nonspecific sign in isolation. Several investigators have used time domain HRV analysis to assess changes before sustained ventricular arrhythmias. Singer and Ori reported in an early study that a time domain measure of HRV fell during the 5-min period immediately preceding ventricular fibrillation (46). Recently, Pozzati et al. (47) reported reductions in SDNN before sustained ventricular arrhythmias, but these were preceded by ST segment shifts due to acute myocardial ischemia and probably do not apply to the current observations. In concert with our observations, other earlier studies have failed to find changes in time domain indices of HRV before VT (48,49).

Frequency domain HRV variables provide more specific information about autonomic activity (24–26). Although the published experience is limited in this area, our results are consistent with the findings of Huikuri et al. (33), who reported significant reductions in frequency domain indices before 12 episodes of sustained monomorphic VT in eight patients. They found that all HRV frequency components were lower before VT compared to nonsustained ventricular tachycardia, and all frequency components demonstrated reduced power compared to the 24-h average in six patients with both sustained and nonsustained ventricular tachycardia. Consistent with our findings and other subsequent investigations, they found that HFP_n did not change before VT. In two subsequent reports, however, these investigators failed to find significant changes in the frequency domain measures of HRV before sustained ventricular arrhythmias (42,49). These inconsistencies may be related to low statistical power due to the small number of subjects (8, 8 and 15 patients with VT, respectively, in three studies [33,42,49]). In addition, studies based on episodes of VT rather than on individual patients could result in a greater influence of those patients with more episodes of VT. Clinical differences in the patients studied is another likely source of differences. Nevertheless, in the study of Valkama et al. (42), LFP was the strongest factor associated with the occurrence of a sustained ventricular arrhythmia on the Holter. Although statistical significance was not achieved, a clear trend for

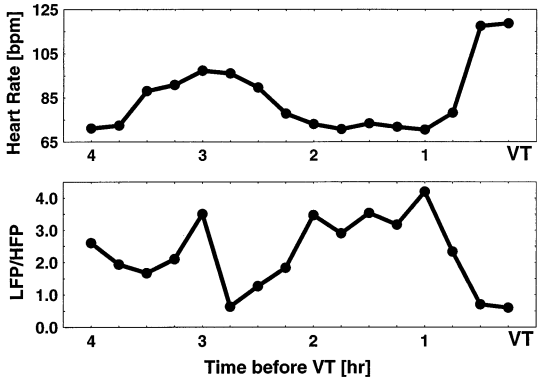


Figure 4. Changes in heart rate (top panel) and the low to high frequency power ratio (LFP/HFP) (bottom panel) during 4 h before ventricular tachycardia (VT) in an individual patient. See text for discussion.

reduction in LFP and VLFP was present before the onset of VT in the two studies (42,49). Moreover, despite the lack of significant changes in HRV preceding sustained spontaneous ventricular arrhythmias, the investigators concluded that changes in autonomic balance are likely to play an important role in initiation of the observed sustained arrhythmias (42,49).

Relation of heart rate and heart rate variability to changes in autonomic nervous system activity before spontaneous ventricular arrhythmias. Withdrawal of parasympathetic nervous system activity has been proposed as an arrhythmogenic mechanism (1,28) and could account for increases in heart rate before ventricular arrhythmias. Time domain measures of heart rate variability may reflect vagal activity (26,28), but none of these variables was found to change significantly before VT. High frequency power, a proposed marker of vagal tone, fell significantly before VT, but the LFP/HFP ratio also declined, indicating a relatively greater drop in LFP. Moreover, HFP_n, a more specific index of parasympathetic activity (25), increased slightly. Furthermore, a significant reduction of vagal tone would be less likely in patients with chronic severe left ventricular dysfunction who are believed to have reduced parasympathetic activity and increased sympathetic tone. These findings do not support withdrawal of vagal activity as the mechanism for increased heart rate or for VT initiation in this group of patients.

The rise in heart rate that preceded VT was most likely due to increased sympathetic activity as proposed in several previous studies (15,19,33). An unexpected but intriguing finding was the paradoxical fall in the low frequency components that accompanied the rise in heart rate. In normal subjects, the LFP/HFP ratio and LFP_n usually rise and fall in concert with heart rate in response to maneuvers that increase and decrease sympathetic activity, respectively (24,25). Instead, we observed a modest decline in LFP_n and LFP/HFP before VT, whereas heart rate increased.

The HRV indices can provide only inferential evidence of the changes in autonomic tone and cannot definitively prove that the mechanism is increasing sympathetic tone and not declining parasympathetic tone or a combination of the two effects. Both increasing sympathetic and decreasing parasympathetic tone would result in a relative increase in sympathetic activity. However, we consider the increasing sympathetic tone to be the most likely mechanism of the observed HRV changes. The drop in LFP was predominant, causing a decrease in the LFP/HFP ratio and an increase in the normalized HFP. The relationships between the sympathetic and parasympathetic effects often do not correspond to the changes in normalized low and high frequency powers (27). Thus an increase in the normalized HFP prior to VT might not indicate the elevated parasympathetic tone, and the diminished parasympathetic activity, as manifested by decreased HFP, cannot

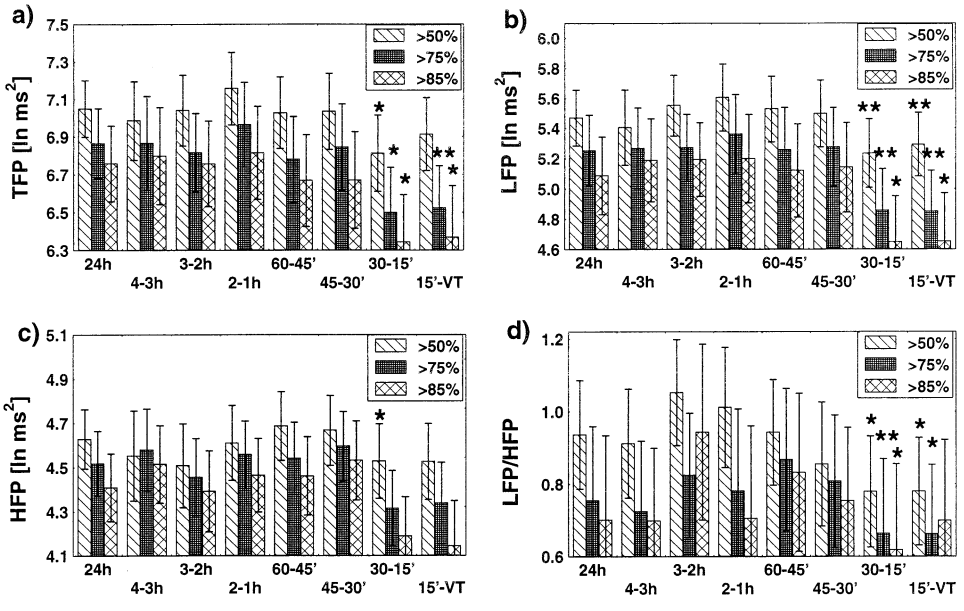


Figure 5. Spectral changes in the total (TFP) **(a),** low frequency (LFP) **(b)** and high frequency (HFP) **(c)** power and low/high frequency ratio **(d)** preceding the arrhythmia with respect to ectopic beat frequency. Power spectral analysis was repeated after removal of data segments not meeting the frequency threshold criteria: >50%, >75% and >85% normal beats. *$p < 0.05$ compared to the 24-h average. **$p < 0.01$ compared to the 24-h average.

be ruled out as a contributing factor in the observed HRV changes.

These paradoxical changes are most likely a consequence of preexisting abnormalities in autonomic function and disturbed response characteristics in patients with chronic severe myocardial dysfunction and ventricular tachyarrhythmias. Evidence for neurohormonal dysfunction has been demonstrated by measurements of myocardial norepinephrine spillover kinetics, an established measure of sympathetic traffic to the heart (50). Myocardial norepinephrine spillover is elevated at rest in patients with left ventricular dysfunction (50,51). Maneuvers that stimulate sympathetic activity, such as exercise and nitroprusside-induced hypotension, cause a rise in norepinephrine spillover, but the response is attenuated in patients with cardiac dysfunction (50,51). Additional evidence for preexisting abnormalities of autonomic function is the chronic depression of LFP despite high resting sympathetic activity in patients with left ventricular dysfunction. The degree of diminution of LFP and other components of HRV have been found to be predictors of mortality after myocardial infarction (30). van de Borne et al. (11) recently demonstrated marked reductions of LFP despite prominent increases of sympathetic nerve activity in patients with severe heart failure. Indeed, patients whose low frequency variability had become undetectable had higher levels of sympathetic nerve activity, lower ejection fractions and greater mortality. Guzzetti et al. (52) showed that the amplitude of the LFP was related to the severity of left ventricular dysfunction. LFP was above normal in patients with increased sympathetic activity associated with mild to moderate left ventricular dysfunction. Patients with more severe cardiac dysfunction, who are known to have higher levels of sympathetic activity, had the lowest values of LFP, consistent with the findings of van de Borne et al. (11). The change in the low frequency component in response to maneuvers that increase sympathetic activity was noteworthy. In contrast to normal subjects, in whom LFP increases with head-up tilt, patients with moderate or severe chronic heart failure demonstrated a marked decrement in LFP (52). A paradoxical decline in LFP in response to exercise was also demonstrated in an animal model of congestive heart failure (53).

The rise in heart rate and fall in LFP, LFP_n and LFP/HFP indicate a paradoxical dissociation between the rise in the average effects of increased sympathetic activity as reflected by increased heart rate, and a fall in the rhythmical effects of increased sympathetic activity, as indicated by the drop in low frequency HRV. These two components become dissociated when their changes approach the limits of physiologic dynamic range (54). Therefore, the dissociation between average and phasic facets of sympathetic activity strongly suggests that sympathetic activity is rising from an already abnormally high level immediately before VT as expected based on measurements of myocardial norepinephrine spillover (50,51). The extent of the rise of sympathetic activity, however, is difficult to estimate, as its physiologic manifestations approach the limits of their dynamic ranges and the signals they generate become saturated. The HRV signal reflects sinus node function. It is important to recognize that the dynamic range of sinus node function is not necessarily the same as other effects of sympathetic activity. Hence the electrophysiologic properties relevant to VT initiation may be undergoing changes in response to rising sympathetic tone that are out of proportion to the changes measured in the HRV signal.

The mechanism of this phenomenon is unknown. It could result from properties intrinsic to the sinus node or extrinsic factors. Proposals include altered sinus node responsiveness to high levels of cardiac sympathetic activation (54), beta-adrenergic receptor down-regulation (11), and compromised central autonomic regulatory functions due to elevated levels of catecholamines, angiotensin or vasopressin (11). Another possible mechanism of this phenomenon is a shift of LFP to the lower frequencies, which was previously found in the same group of patients (55,56).

There are diurnal variations in the occurrence of ventricular tachycardia and HRV (57–59). In this group, the frequency of VT was higher during day than during night, peaking in the morning and late afternoon. These peaks coincided with the peaks of the 24-h heart rate distribution in this group and the reported peaks of plasma catecholamine concentration (60,61). Thus circadian changes in the autonomic activity could have an impact on the changes in heart rate and heart rate variability preceding VT in some patients. However, the drop in LFP before the onset of arrhythmia did not correspond to the morning increase in LFP in patients with congestive heart failure (58) and survivors of cardiac arrest (59). The circadian changes in HRV are severely diminished in this population and do not demonstrate any pronounced variations in LFP, which might resemble those before the onset of VT (62). This suggests that circadian variations taken in isolation cannot be a sole factor causing the changes in heart rate and HRV before VT.

Although LFP reflects autonomic modulation of the cardiac cycle, other physiologic processes, including arterial pressure and muscular sympathetic nerve activity, demonstrate modulation at the same frequency and tight correlation to HRV in response to interventions that change autonomic tone (25,63). Thus LFP may reflect systemic effects of autonomic nervous system function. Our findings, and the work of others, demonstrate the dual nature of autonomic activity, that is, its average and rhythmical components (11,64). The average component is manifested not only as heart rate, but also as the burst rate of muscular sympathetic nerve activity (11,63). The phasic component is manifested as the LFP in the HRV signal as well as other physiologic processes, including variabilities of arterial pressure, muscular sympathetic nerve activity, temperature and vasomotor activity (11,57,63,65,66).

Limitations. Our study is subject to several important limitations. Changes in heart rate prior to the onset of VT might violate the assumption of stationarity of the signal, which is required in conventional spectral analysis. However, analyses performed at both 5- and 15-min segments suggested that transients resulting from changes in heart rate did not contrib-

ute significantly to the findings. Application of the Hanning window prior to the spectral analysis also attenuates the effects of nonstationarities and discontinuities. A more important limitation is that our observations are based on post hoc analyses of data recorded on 24-h electrocardiograms, and there was no opportunity to measure autonomic nervous system activity by more direct techniques that could corroborate our findings. The results of HRV analysis could be affected by several factors, including the organic heart disease, the gain of interaction between the neural activity and the sinus node, humoral milieu, receptor transduction properties and different respiration patterns. The impact of these factors could not be examined in this study.

Moreover, in a strict sense, our findings apply only to the population represented by the subjects selected. In most of the patients we studied the presenting arrhythmia did not result in ventricular fibrillation, and a minority required an acute intervention to terminate the arrhythmia (17). On the other hand, the subset of the clinical trial patients selected for this analysis did not differ significantly from the other patients in the ESVEM trial with respect to clinical or outcome variables (17). Many characteristics of the patients we studied are similar to those in previous studies of ambulatory recordings obtained in patients who died suddenly or had cardiac arrests and which provided evidence of the contribution of increasing sympathetic drive to arrhythmogenesis (19). Further research will be required to determine if our findings apply to other groups of patients at risk for ventricular tachyarrhythmias.

The alterations in HRV indices that preceded the onset of VT were observed at other times during the 24-h recordings. This supports the concept that multiple factors contribute to arrhythmogenesis and justifies a multicomponent approach to the prediction of VT (67).

Conclusions. We conclude that alterations in autonomic activity precede the onset of sustained ventricular tachycardia in some patients. The changes in HRV cannot be linked to a specific change in autonomic activity with certainty, and a causal relation to the onset of VT cannot be proven in the context of this study. Nevertheless, instead of the parallel rise in average and rhythmical manifestations of increased sympathetic activity seen at low or moderate levels of sympathetic stimulation in normal subjects, we found spontaneous dissociation of these two facets of autonomic activity immediately before the onset of ventricular tachyarrhythmias. This mismatch of phasic and average components of altered neurohormonal activity appears to be a sign of a critical aspect of the arrhythmogenic process, and it may be a crucial contributor. If so, it may be possible to use this phenomenon to predict impending arrhythmic events, and it could be an important target for antiarrhythmic protection.

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